REMARKS/ARGUMENTS

Claims 1, 4-7 and 23 are pending in the application. In the present amendment claim 1 has been amended to correct the grammar of the claim. No new matter is introduced by way of the claim amendment.

Priority

As discussed in the previous amendment, the trkC sequence of SEQ ID NO: 6 is found in the priority application Serial No. 08/215,139 filed on March 18, 1994, in which the use of trkC antibodies for the treatment of axonal sprouting in epilepsy is also mentioned (*e.g.*, page 88, lines 6-7). Accordingly, applicants reiterate their conclusion that the priority date of the present application is March 18, 1994.

Rejections

Claims 1, 4-7, and 23 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Claims 1, 4-7, and 23 stand rejected for alleged lack of written description. These rejections are respectfully traversed.

The Rejections of Claims 1, 4-7, and 23 Under 35 U.S.C. §112, First Paragraph

Claims 1, 4-7, and 23 stand rejected as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

In support of the rejection, the Examiner refers to: (1) the existence of truncated and variant forms of trkC receptors as well as full-length trkC receptors (page 3, lines 9-11); and (2) the alleged lack of nexus between "any particular trkC of SEQ ID NO:6 and aberrant sprouting and any disease" (page 3, lines 17-18 of the Office Action dated July 23, 2004). Although the Examiner acknowledges the specification's teaching that antagonists of trkC are believed to be useful for treating aberrant neuron sprouting in epilepsy (sentence bridging pages 4 to 5 of the Office Action), she states that "there is no explanation as to why this statement is made," and points to an alleged lack of teaching as to which of the various forms of trkC receptor is involved in aberrant sprouting.

Applicants note that the art recognized that there was a relationship between trkC, NT-3, neuronal sprouting, and epilepsy at the time the application was filed. For example, as discussed in

more detail below, it was recognized that neuronal sprouting occurred in epilepsy, that there was a relationship between NT-3 and neuronal sprouting (and thus a relationship between NT-3 and epilepsy), and that there was a relationship between trkC and epilepsy. This recognition in the art at the time the application was filed, taken with the statement in the specification at page 68 that "[t]his antagonist activity is believed to be useful in the treatment of pathological conditions associated with endogenous neurotrophin production, such as ... aberrant sprouting in epilepsy ..." would be understood by one of ordinary skill in the art to provide an explicit connection between a trkC of SEQ ID NO: 6, aberrant neuronal sprouting, and a disease (epilepsy).

For example, applicants draw the Examiner's attention to Babb et al., 1991 ("Synaptic Reorganization by Mossy Fibers in Human Epileptic Fascia Dentata," *Neuroscience* **42**:351-363 (1991)) in which new synapse formation was found in hippocampal tissue removed from human epileptic patients. No evidence of similar new synapse formation was found in matched autopsy tissue from non-epileptic humans. Similar evidence had been reported, for example, by Represa et al. ("Sprouting of Mossy Fibers in the Hippocampus of Epileptic Human and Rat" Excitatory Amino Acids and Neuronal Plasticity, Ed. Ben-Ari, Plenum Press, New York, 1990 pages 419-424) and the topic was reviewed by Ben-Ari and Represa ("Brief seizure episodes induce long-term potentiation and mossy fibre sprouting in the hippocampus," *Trends in Neurosciences* **13(8)**:312-318 (1990)) and by Babb ("Axonal Growth and Neosynaptogenesis in Human and Experimental Hippocampal Epilepsy," *Advances in Neurology* Vol. 72, Neuronal Regeneration, Reorganization, and Repair, edited by Frederick Seil, Lippincott-Raven Publishers, Philadelphia, 1997, Chapter 5, pages 45-51). Thus, it was recognized by the early 1990s that neuronal sprouting was found in epilepsy. Such knowledge has been corroborated since the time of filing; for example, see Scharfman ("Epilepsy as an Example of Neural Plasticity" *The Neuroscientist* **8(2)**:154-173 (2002)) which, in discussing neuronal sprouting, notes that "[p]erhaps the most widely studied and remarkable example is the sprouting or mossy fibers after seizures" (page 162, column 1, lines 27-28).

Similarly, a relationship between sprouting and trkC and NT-3 was known. See, for example, Bengzon et al., "Regulation of Neurotrophin and *trkA, trkB* and *trkC* Tyrosine Kinase Receptor Messenger RNA Expression in Kindling," *Neuroscience* **53(2)**: 433-446 (1993), and related discussion in McNamara, "Cellular and Molecular Basis of Epilepsy," *J. Neuroscience*

14(6):3413-3424 (1994), page 3419, showed that trkC and NT-3 were each altered in animal models of seizure activity. Thus, it was known in the art at the time the application was filed that trkC levels were changed by seizures, and thus that methods affecting trkC or NT-3 levels or activity would be expected to be useful to affect neuronal sprouting, of use in treating epilepsy. This has been corroborated by such findings as that local increases in NT-3 can induce sprouting (Zhou et al., "Neurotrophin-3 Expressed *In Situ* Induces Axonal Plasticity in the Adult Injured Spinal Cord," *J. Neuroscience* **23(4)**:1424-1431 (2003)).

In addition, applicants note that Claim 1 recites "an antagonistic antibody specifically binding to a sequence within amino acid residues 32 and 839 of SEQ ID NO: 6." Thus, the claim recites a particular region of the identified sequence, and clearly identifies and limits the claimed invention to methods using antibodies directed to this specific portion of the explicitly identified amino acid sequence.

The Examiner's allegation that "no nexus has been established between any particular trkC of SEQ ID NO: 6 and aberrant sprouting in any disease" (page 3, lines 16-18) is thus seen not to reflect the state of the art at the time the application was filed. As discussed above, a relationship between trkC and aberrant sprouting, and between trkC and disease conditions in which aberrant sprouting occurs (e.g., epilepsy) was well recognized at that time. Applicants explicitly disclosed that trkC antagonist antibodies are useful in treating pathological conditions associated with aberrant sprouting in epilepsy (page 68, lines 24-29). Accordingly, a nexus was established between a trkC of SEQ ID NO: 6 and aberrant sprouting in epilepsy, at least, and would have been recognized as such by one of ordinary skill in the art.

In addition, Applicants note that the method of claim 1 requires an antibody that specifically binds to "a sequence within amino acid residues 32 and 839 of SEQ ID NO: 6." Such an antibody will specifically bind the full-length human trkC receptor, and, as recognized by the Examiner, will specifically bind other splice variants of the human trkC receptor. The recognized relationship between trkC, aberrant sprouting, and a disease in need of treatment being clear, the Examiner's concern that a "particular trkC" need be identified is believed to be unwarranted, for at least the reason that, for any particular antibody, such splice variants will fall into one of only two possible groups: (a) those splice variants that include an amino acid sequence bound by the antibody, and (b) those splice variants that <u>do not</u> include an amino acid sequence bound by the antibody. The

claimed method is clearly applicable and enabled for human trkC receptors of group (a), at least because such binding would be readily ascertainable by one of ordinary skill in the art without undue experimentation. Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

The Federal Circuit has also noted: "We agree with the district court's conclusion on enablement. Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid." *Atlas Powder Co. v. E. I. du Pont de Nemours & Co.* 750 F.2d 1569, 1576 224 USPQ 409, 414 (Fed. Cir. 1984). Applicants respectfully submit that one of ordinary skill in the art would know, without undue experimentation, whether antibodies that specifically bind to a sequence within amino acid residues 32 and 839 of SEQ ID NO: 6 were indeed binding to such a sequence and so were useful for the practice of the invention to inhibit neuronal sprouting and to treat pathological conditions associated with elevated NT-3. Methods of treatment are discussed, for example, at pages 69-71, and elsewhere in the specification. It would have been within the skill of one reading the application to practice the invention without unduly excessive experimentation.

Similarly, the lack of specific binding to the human trkC receptor splice variants of group (b) would be readily ascertainable by one of ordinary skill in the art without undue experimentation. Thus, if a human trkC splice variant lacks a sequence required by such an antibody, one of ordinary skill in the art would know, without undue experimentation, that in that instance the antibodies did not specifically bind. As discussed in *Atlas Powder*, such lack of binding in no way indicates that the claim is not enabled.

Thus, despite the Examiner's allegation that "no nexus has been established between any particular trkC of SEQ ID NO: 6 and aberrant sprouting in any disease" (page 3, lines 16-18), it is clear that the art recognized a nexus between trkC and aberrant sprouting with respect to the disease of epilepsy at the time the application was filed, and that the applicants have identified the human trkC receptor of SEQ ID NO:6 to which the invention is directed.

As discussed previously, applicants note that the claims are directed to the use of antibodies specifically binding the full-length trkC receptor of SEQ ID NO: 6, without the associated signal sequence, so that any issues concerning the potentially different biological activities of the various splice forms no longer apply. An antagonistic antibody of the invention must specifically bind to a

sequence within the amino acid residues 32 and 839 of SEQ ID NO: 6. The specification teaches such trkC receptors; as discussed above, such receptors would have been expected to be related to neuronal sprouting in epilepsy, and so such treatment would be expected to be useful and effective in such treatment. The specification provides guidance for such treatments, for example, at pages 69-71. Applicants submit that one of ordinary skill in the art, following the teachings of the specification, in view of the state of knowledge in the field, would have been enabled to make and use the invention.

Applicants respectfully submit that one of ordinary skill in the art would indeed believe it more likely than not that the invention would function as claimed when taken in view of the knowledge of one of ordinary skill in the art at the time that application was filed and would be enabled to produce the claimed antibodies and to treat the conditions for which they are taught to be useful.

In addition, the Examiner suggests that there might be issues related to overexpression of non-productive trkC in adults compared with productive trkC, and to effects of such nonproductive trkC on the methods as claimed (page 5, lines 14-16). The Examiner is apparently referring to the Examiner's statement in the Office Action mailed January 15, 2004 regarding "the number of tissues, including the nervous system that apparently express non-productive receptors that do not comprise a TK domain. In particular, the specification suggests that the role for the truncated forms of the trks is to act as a dominant negative influence signal on signal transduction by neurotrophin expressing cells" the Examiner going on to suggest that "The effect of this upon sequestration of the antagonistic antibody cannot be predicted." (Office action mailed January 15, 2004, page 11, lines 2-7.)

However, even if one accepts that such "non-productive" receptors do act to sequester the antagonistic antibodies of the invention, one can of course predict that the effect of such sequestration would likely affect the dosage of the antagonistic antibodies needed, as would non-specific binding or the activity of any of the well-known clearance mechanisms associated with *in vivo* delivery of any therapeutic agent. Such effects are well known, and may be accounting for by routine experiments that are well within the skill of one of ordinary skill in the art. Such experimentation is not undue, but is instead well within the normal course of events and is expected in the use of all treatments.

Applicants submit that based on the teaching of the specification one skilled in the art is able to make and use the invention claimed without undue experimentation. Accordingly, applicants respectfully request the withdrawal of the rejections of claims 1, 4-7 and 23 under 35 U.S.C. § 112, first paragraph as allegedly not enabled.

The Rejections of Claims 1, 4-7, and 23 Under 35 U.S.C. §112, First Paragraph

Claims 1, 4-7, and 23 stand rejected for alleged lack of written description in the specification. The rejection of the remaining claims is respectfully traversed.

The Examiner suggests that the cases *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), hereafter "Lilly," and *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002), hereafter "Enzo," are applicable in the present case. In addition, the Examiner suggests that there has been "no nexus made between any trkC sequence and aberrant neuron sprouting, no nexus made between trkC and epilepsy, there is no description of the structure of the population of cells associated with neuron sprouting" and that the lack of such description means that the specification "cannot adequately describe a method of inhibiting aberrant neuron sprouting" (page 6, lines 10-11). The Examiner also suggests that a representative number of trkC antagonists is lacking in the specification (page 6, lines 13-14). Applicants respectfully traverse these rejections.

As discussed above, the nexus between neuron sprouting and epilepsy was well-known at the time the application was filed (see, *e.g.,* Ben-Ari and Represa, *Trends in Neurosciences* **13(8)**:312-318 (1990)) as was the nexus between trkC and epilepsy (*e.g.,* Bengzon et al., *Neuroscience* **53(2)**: 433-446 (1993) and McNamara *J. Neuroscience* **14(6)**:3413-3424 (1994), page 3419, discussed above). The cells shown to exhibit aberrant sprouting in epilepsy are hippocampal dentate granule cells, well-known to be the cell bodies which give rise to the mossy fibers that sprout, *e.g.,* in the CA3 region of the hippocampus, as was well-known at the time of filing as discussed in the references cited above.

The Examiner further alleges that "although the specification mentions antagonists of trkC the specification fails to describe a representative number of such species" (page 6, lines 12-14). However, the claimed antagonists are antibody antagonists, and the amino acid sequence to which these antibody antagonists are directed is SEQ ID NO: 6. Preparation of antibodies is described in the specification, for example, at pages 56-66, and preparation of immunoadhesins is described, for

example, at pages 49-56. In addition to the detailed methods disclosed in the specification, antibody preparation was within the knowledge and skill of one of ordinary skill in the art at the time the application was filed.

The Examiner, however, alleges that "the instant claims are drawn to naming a type of material generally known to exist in the absence of knowledge as to what the material consists of" (page 6, lines 5-6) and cites Lilly and Enzo as thus being relevant to the present situation. However, despite the Examiner's assertion, applicants respectfully submit that there is no "absence of knowledge as to what the material consists of."

The claimed antagonistic antibodies are all directed to, and specifically bind to, "a sequence within amino acid residues 32 and 839 of SEQ ID NO: 6." This is not a case of "absence of knowledge." The present application does not present a case where a claimed nucleotide sequence is ambiguous by being defined from an amino acid sequence and where the degenerate genetic code provides multiple possibilities; in the present case the amino acid sequence to which the antagonistic antibodies are directed is known and disclosed, and methods for making the antagonistic antibodies of the claims are taught in the specification. In particular, the Lilly and Enzo cases are not applicable where, as here, a specific amino acid sequence is recited, and antibodies that specifically bind to that sequence are utilized in the claimed methods.

In addition, as discussed above (see, *e.g.,* Bengzon et al.; Ben-Ari and Represa; and other references), the nexus between trkC and aberrant sprouting is clear; the nexus between trkC and epilepsy is clear, and follows from the known nexus between aberrant sprouting and epilepsy; the population of cells associated with aberrant neuronal sprouting was known, so that an identified population of cells to treat was recognized; and the trkC sequence of SEQ ID NO: 6 is disclosed in the specification. Accordingly, taken in view of the knowledge of one of ordinary skill in the art, and in view of the explicit disclosure of the amino acid sequence to which the antibodies are directed and of the disclosure relating to antibody production and preparation, the specification provides an adequate written description of the claimed invention.

CONCLUSION

All claims pending in this application are believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** (**Attorney's Docket No. 39766-0033 CPC4C**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully Submitted,

Date: December 21, 2004

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